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CERTIFICATE OF MAILING BY FIRST CLASS MAIL (37 CFR 1.8) Applicant(s): Alberto L. Mendoza			Docket No. MSU 4.1-406	
Application No.	Filing Date	Examiner	Customer No.	Group Art Unit
09/082,112	May 20, 1998	Brian J. Gangle	21036	1645

Invention: **METHOD AND VACCINE FOR TREATMENT OF PYTHIOSIS INSIDIOSI IN HUMANS AND LOWER ANIMALS**

I hereby certify that this **REPLY BRIEF**

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Alberto L. Mendoza
Serial No.:	09/082,112
Filed:	May 20, 1998
Title:	METHOD AND VACCINE FOR TREATMENT OF PYTHIOSIS INSIDIOSI IN HUMANS AND LOWER ANIMALS
Examiner:	Brian J. Gangle
Group Art Unit:	1645
Confirmation No.:	2322
Customer No.:	21036
Attorney Docket No.:	MSU 4.1-406

REPLY BRIEF

MS Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This reply brief is filed in response to the examiner's answer mailed December 22, 2008 ("Examiner's Answer") for the pending appeal in this application.

Any fee deficiencies may be charged, or any overpayment credited, to our deposit account 13-0610.

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I. Status of Claims

The status of the claims remains as set forth on page 3 of the appeal brief filed on September 11, 2006 ("Appeal Brief") and as modified on pages 2-3 of the Examiner's Answer: claims 16-23 are pending and stand rejected as obvious.

II. Grounds of Rejection to be Reviewed on Appeal

The grounds for rejection to reviewed on appeal remain as set forth on pages 6-7 of the Appeal Brief: whether claims 16-24 are obvious over Mendoza 92a, Mendoza 92b, Mendoza 95, the Amicon catalog, and the Fisher catalog, further in view of Mendoza 96 or Blanch.[1]

This Reply Brief is specifically presented to address arguments in the Examiner's Answer with respect to the following issues on appeal:

> (1) whether the combined references teach or suggest the removal of low molecular weight components less than 10,000 MW;
>
> (2) whether the combined references teach or suggest a vaccine having all of the larger molecular weight components; and
>
> (3) whether the combined references teach or suggest administering the recited vaccine to humans.

[1] Specific citations for the references of record are provides on pages 6-7 of the appeal brief.

III. Argument

A. Removal of Low Molecular Weight Components (Issue 1)

Claims 16 and 18 recite that the mixture of intracellular and extracellular proteins "has been dialyzed to remove low molecular weight components less than 10,000 MW."

The examiner's answer asserts that this limitation is taught by Mendoza 92b, Amicon, and Fisher. Examiner's answer, p. 5-6.

Mendoza 92b discloses the immunoblot analysis of *Pythium insidiosum* and *Conidiobolus coronatus*. Intracellular proteins from *P. insidiosum* were recovered from the supernatant of sonicated and centrifuged cell mass. Mendoza 92b, p. 2981, col. 1, ¶ 1. Proteins from *C. coronatus* were concentrated by ultrafiltration (using an Amicon PM-10 membrane) of a *C. coronatus* culture filtrate.

Even though Mendoza 92b discloses the Amicon PM-10 membrane (which retains molecules larger than 10,000 MW according to the Amicon reference), Mendoza 92b *only* does so in the context of concentrating *C. coronatus* proteins. Thus, Mendoza 92b (and the remaining references in combination) fails to teach or suggest the removal low molecular weight components less than 10,000 MW from *P. insidiosum* proteins as recited.

Further, there is no reason that the skilled artisan would have applied the PM-10 membrane ultrafiltration to the *P. insidiosum* proteins in view of the teachings of Mendoza 92b. The PM-10 membrane was used to concentrate a *C. coronatus* culture filtrate in Mendoza 92b. However, Mendoza 92b's *P. insidiosum* proteins were concentrated in a clarified supernatant by the disclosed centrifugation step, so there would have been no reason to include a redundant membrane filtration (or dialysis) step in view of the combined references.

Thus, the appellant submits that the applied references fail to teach or suggest all recited limitations, and there can be no *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988) (requiring that each and every limitation of a claim is described or suggested by the prior art, or would have been

obvious based on the knowledge of those of ordinary skill in the art, to support a *prima facie* conclusion of obviousness); MPEP § 2143.

B. Vaccine Having All Larger Molecular Weight Components (Issue 2)

Claims 16, 18, and 19 recite providing a vaccine that is obtained by specific process steps. In particular, intracellular proteins removed from the supernatant[2] of disrupted *P. insidiosum* cells are mixed with extracellular proteins, and the mixture is precipitated with acetone and dialyzed to remove low molecular weight components less than 10,000 MW.

Because the recited vaccine is obtained by recited process steps, the composition resulting from the process steps should be considered when evaluating whether the vaccine is disclosed, taught, or suggested by the applied references. *See* MPEP § 2113 (product-by-process claims are limited by the structure implied by the process steps) (*citing In re Garnero*, 412 F.2d 276, 279 (CCPA 1979)). Thus, the resulting recited vaccine includes a plurality of intracellular proteins above 10,000 MW (or 10 kDa), and not just the three immunodominant antigens at 28 kDa, 30 kDa, and 32 kDa. *See* Mendoza 92b, p. 2981-82 (disclosing a similar process for obtaining intracellular proteins and illustrating a plurality of bands between at least about 14 kDa and 97 kDa in Figures 1 and 2).

Mendoza 92a discloses two vaccines: (1) a cell-mass vaccine (CMV) including intracellular proteins and (2) a soluble concentrated antigen vaccine (SCAV) including extracellular proteins. Mendoza 92a, p. 90-91. However, Mendoza 92a teaches that the SCAV is strictly superior to the CMV. Specifically, (1) the CMV has more prominent inflammatory side effects than the SCAV, (2) the CMV has a much shorter shelf-life than the SCAV, and (3) the effectiveness of the SCAV in curing horses infected with *P. insidiosum* is essentially the same as or better than the CMV at any point during the development of the infection (i.e., as measured by the age of *P. insidiosum* lesions). *Id.*, p. 89 (abstract) and p. 92 (Table 1). As a

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[2] The "supernatant" limitation is recited in independent claim 16 and claim 19 depending from claim 18. Accordingly, the arguments in this section apply as well to claim 19, which claim is separately argued.

result, Mendoza 92a recommends using only the SCAV to treat a *P. insidiosum* infection. *Id.*, p. 89 (abstract).

Mendoza 95 discloses that the effectiveness of Mendoza 92a's SCAV can be improved by adding the three immunodominant antigens at 28 kDa, 30 kDa, and 32 kDa to the vaccine. Mendoza 95, abstract; Mendoza 96, p. 161, col. 1.

Thus, the combined references fail to teach or suggest a vaccine having all of the larger molecular weight intracellular components as implied by the product-by-process vaccine recited in the claims. Mendoza 95 only suggests an improved vaccine that includes only three specific intracellular proteins (i.e., 28 kDa, 30 kDa, and 32 kDa) added to the extracellular SCAV. Mendoza 95 does not teach or suggest the inclusion of intracellular proteins ranging from 10 kDa to 28 kDa or above 32 kDa and does not teach or suggest the recited intracellular vaccine components.

Moreover, there is no reason that the skilled artisan would include a full range of the larger molecular weight intracellular components with the extracellular SCAV based on the teachings of Mendoza 92a. Mendoza 92a teaches that the intracellular CMV, which is not limited to any particular molecular weight range, is both the source of the adverse vaccine properties (i.e., more prominent side effects and short shelf-life) and does not offer any advantage in terms of treatment efficiency.

As a result, the skilled artisan would have no reason to "optimize" the relative amounts of intracellular and extracellular proteins in a mixed vaccine, and thus the skilled artisan could not have arrived at the claimed methods without impermissible hindsight. Given the strictly inferior characteristics of the intracellular CMV compared to the extracelluar SCAV, the would not have been a reason to augment the SCAV with anything more that the three specific immunodominant intracellular proteins. Accordingly, the applied references teach away from the claimed methods because the skilled artisan "would be led in a direction divergent from the path that was taken by the applicant." *In re Kahn*, 441 F.3d 977, 999 (Fed. Cir. 2006).

The appellant submits that the foregoing presents an additional, independent for reversing the obviousness rejection of the pending claims.

C. Vaccine Administration to Humans (Issue 3)

Part (b) of claim 16 recites vaccinating a human patient with the vaccine from part (a) of the claim.[3]

Even though the Mendoza references are collectively limited to the administration of vaccines to horses, the examiner's answer asserts that Mendoza 96 teaches (1) similarity in *P. insidiosum* antigens detected in human and horse sera and (2) similarity in human and animal pythiosis infections. Examiner's answer, p. 13-14.

The appellant respectfully submits that the relied-upon portions of Mendoza 96 do not suggest administering the equine vaccines from the earlier Mendoza references to humans infected with *P. insidiosum*.

Mendoza 96 is an academic review article addressing *P. insidiosum* infections. As such, Mendoza 96 addresses a broad range of topics not specifically related to treating *P. insidiosum* infections (e.g., morphology, epidemiology, pathogenesis, affected animals) in addition to animal-specific methods of treatment. Mendoza 96 teaches that "the pathogenesis of pythiosis insidiosi has not been fully delineated" and further that the general lack of understanding is partly based on the inability to reproduce the infection in animal models (e.g., horses). Mendoza 96, p. 155, col. 1 (pathogenesis) and p. 160, col. 1 (animal studies). Additionally, while human and equine cases of pythiosis insidiosi have histological similarities, there are differences between the two diseases. *See* Mendoza 96, p. 156, col. 1 to p. 157, col. 2 ("But, kunkers, as encountered in equine pythiosis insidiosi, were not detected in tissue from this and other human cases.").

Mendoza 96 teaches that there are three therapeutic methods for treating *P. insidiosum* infections: surgery, chemotherapy, and immunotherapy (i.e., vaccination). Mendoza 96, p. 160, col. 2. Surgery is applicable to the treatment of equines, dogs, and humans, while chemotherapy is applicable to equines and humans. *Id.*, p. 160, col. 2 to p. 161, col. 1. Notably, however, Mendoza 96's entire section related to

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[3] Claim 16 recites "(b) vaccinating *human the patient* with the vaccine" (emphasis added). The appellant submits that the intent of the claim is clear and the language can be suitably amended for clarity if the obviousness rejection is reversed and the application is remanded to the examiner (e.g., "(b) vaccinating ~~human~~ the human patient").

immunotherapy is limited to the treatment of equines, for example with the vaccines of Mendoza 92a and Mendoza 95. *Id.*, p. 161, col. 1 to p. 162, col. 1. Mendoza never suggests the use of vaccines in humans and specifically indicates that "there are no records of these vaccines being used in other domesticated animals or in humans." *Id.*, p. 161, col. 2. Mendoza 96 further teaches that the mechanism of the immune response of equines to vaccination is unclear, but hypothesizes that the mechanism is related to the structural kunker feature of the equine infection. *Id.*, p. 161, col. 2 and p. 162, col. 1 (Figure 9).

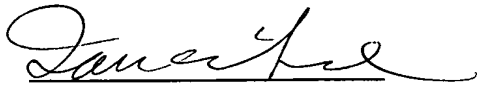
In view of the foregoing, Mendoza 96 simply provides the skilled artisan with no reason to administer the earlier Mendoza equine vaccines to humans. Mendoza 96 only discloses surgery and chemotherapy as treatment options for humans. Despite the relative success of vaccines in treating equines, Mendoza 96 never discloses or even suggests that immunotherapy might be effective in humans or even in any other non-equine animals. Given the unclear pathogenesis and unclear mechanism for vaccine operation in equines, there is no basis to extrapolate the successful equine treatment to humans. Even the hypothesized mechanism for vaccine operation in equines is substantially related to the presence of kunkers, a histological feature of the equine infection that is completely absent in human infections. This further limits the potential extrapolation of equine vaccination data to human treatment.

In view of the foregoing, the appellant submits that the applied references do not teach or suggest the administration of vaccines to humans as a treatment for *P. insidiosum* infections. Accordingly, the appellant requests reversal of the obviousness rejection of claim 16 for this additional, independent reason.

D. Conclusion

In view of the foregoing and the previously submitted appeal brief, the appellants submit that claims 16-24 are not obvious over the applied references. Accordingly, the appellants respectfully request reversal of the 35 USC § 103 rejections.

Respectfully,



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